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Review

Current treatment approaches in the management of the heart failure patient

Bilgin Bahadır Başgöz[1], Cansu Öztürk[2], Caner Varhan[3], İhsan Solmaz[3]

[1]Department of Internal Medicine, Gülhane Faculty of Medicine, University of Health Sciences, Ankara, Turkiye
[2]Department of Cardiology, Gazi Yaşargil Training and Research Hospital, University of Health Sciences, Diyarbakır, Turkiye
[3]Department of Internal Medicine, Gazi Yaşargil Training and Research Hospital, University of Health Sciences, Diyarbakır, Turkiye

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Corresponding Author: Caner Varhan, drcvarhan@gmail.com

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ABSTRACT

Heart failure is a clinical syndrome in which the function of the heart muscle and neurohormonal regulation are impaired, resulting in an inability to meet the metabolic needs of tissues. Many different mechanisms are involved in the pathophysiology of heart failure. Therefore, this disease is defined as a chronic disease in which treatment management is difficult for both the patient and the physician. Therefore, although the main goal is to take the necessary precautions before the disease develops, this may not always be possible. The management of the disease and the treatment options are being provided by finding drugs that are effective against existing mechanisms or against new mechanisms that have been discovered. The main goal of treatment is to stop the chain of events that cause and worsen heart failure based on the physiopathology. For this reason, there are various treatment modalities accepted in current guidelines to manage the current process. The aim of these treatments is to reduce symptoms, improve quality of life, and reduce mortality and morbidity rates. Recently, many important developments in the field of heart failure have started to come one after another. In this article, the mechanisms of action of the current treatment options and their effects on mortality have been mentioned, but rather than the current pharmacologic treatments, promising new treatment options, especially phase 3 and phase 4 trials, have been evaluated.

Keywords: Heart failure, current treatment, medications, phase trials

INTRODUCTION

Heart failure (HF), to which millions of new cases are added every year, is still one of the most important health problems, despite improved diagnostic and therapeutic methods. In 2019, estimated 56.2 million people were living with HF across 204 countries globally, although the estimate likely underrepresents the true prevalence of HF because of data and diagnostic gaps in low-resource regions.[1] Despite high treatment costs, 1 out of every 2 patients diagnosed with HF dies within the following 5 years, and 1 out of every 3 patients hospitalized for HF dies within the following year. Therefore, it is very important to take the necessary preventive measures before the development of HF and to ensure that it is treated effectively for a long time after its development.

The primary goals of HF treatment are to reduce symptoms, improve quality of life and functionality, and reduce hospitalization and mortality. To achieve these goals, all factors that have an impact on the disease process and outcomes, such as lifestyle modification, identification and treatment of comorbidities, determination of the stage of the disease, and appropriate pharmacological and/or device therapies, should be addressed by a knowledgeable and experienced clinical team, and all of them should be effectively combated.

Considering the breadth of the subject and the existence of international consensus reports, this article will focus mainly on promising new treatment options rather than current pharmacological treatments.

CURRENT PHARMACOLOGIC TREATMENT AGENTS IN HEART FAILURE

Management of risk factors such as smoking and alcohol use, obesity, hypertension and diabetes mellitus, which have proven adverse effects on outcomes, is the first line of treatment in patients with HF.

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2I)

SGLT2i is suggested for people with symptoms of reduced ejection fraction HF (HFrEF) to lower the risk of hospitalization and death from cardiovascular disease, even if they also have type 2 diabetes. Following recent updates,

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SGLT2i has also become the primary treatment option in patients with HF with preserved ejection fraction (HFpEF).[2]

Angiotensin Receptor-Neprilysin Inhibitors (ARNI)

Neprilysin, a neutral endopeptidase, mediates the degradation of many endogenous vasoactive peptides, especially natriuretic peptides, and decreases their levels. Sacubitril, an inhibitor of neprilysin, decreases the degradation of vasoactive peptides by inhibiting neprilysin and increasing their blood levels. This prevents water and sodium retention, vasoconstriction, and neurohumoral overactivation, leading to inappropriate remodeling.

In the PARADIGM-HF trial, sacubitril/valsartan, an ARNI, was shown to be superior to enalapril in reducing hospitalizations for worsening HF, CV mortality, and all-cause mortality in patients with LVEF≤40% (HFrEF).[2] In recent heart failure guidelines, ARNI has taken its place as the RAASi of first choice with a high level of evidence.

Angiotensin Converting Enzyme Inhibitor (ACE-I)

Effective dose ACE-I use has been shown to reduce mortality and morbidity in patients with HFrEF. Therefore, its use is recommended with a high level of evidence in all patients with CHF who cannot use ARNI, who have no contraindications for ACE-I use, and who can tolerate ACE-I. In survivors of acute MI with asymptomatic LV dysfunction (LVEF<35%-40%), RCTs have shown that ACEi reduced mortality, HF hospitalizations, and progression to severe HF compared with placebo.[3,4]

Beta Blocker (BB)

BB and ACE-I are known to have complementary effects and are recommended to be used together in patients with HF unless there is an obstacle. In combination, these two classes provide a comprehensive neuroendocrine blockade targeting both the heart, where beta blockade reduces cardiac output, and the vessels, where ACE inhibition induces vasodilation among other actions.[5] Carvedilol, extended-release metoprolol, nebivolol, and bisoprolol are the main molecules that have been shown to increase the duration of the symptom-free period and survival and are recommended for use in HF indications.

Angiotensin Receptor Blocker (ARB)

Although they are widely used, they are only recommended as an alternative for patients who cannot tolerate ACE-I. ARBs have significantly lower withdrawal rates than ACEi and most of the ARBs are nearly as effective as ACEi in the treatment of HF.[6]

Mineralocorticoid Receptor Antagonists (MRA)

Evidence has shown that aldosterone and MR activation may play a significant role in cardiovascular events.[7] MRAs (Spironolactone or Eplerenone) are recommended to reduce mortality and HF-related hospitalization in patients with persistent HF-related symptoms and left ventricular ejection fraction (EF)≤35% as measured by echocardiography despite receiving optimal doses of ACE-I and BB therapy.[8]

Eplerenone causes less gynecomastia development because it causes a more specific aldosterone blockade. Patients given MRA should be closely monitored, especially in terms of renal function and hyperpotassemia.

Diuretics

Expansion of extracellular fluid volume is central to the pathophysiology of heart failure. Increased extracellular fluid leads to elevated intracardiac filling pressures, resulting in a constellation of signs and symptoms of heart failure referred to as congestion.[9]

Although their positive effects on mortality and morbidity have not been demonstrated in randomized controlled trials, they have been used for a period of time in almost all patients, mainly loop diuretics and thiazides, to reduce the signs and symptoms of fluid overload.

Diuretics are recommended for HF patients with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalizations.[2]

The ADVOR study showed a significant increase in the incidence of successful decongestion within 3 days with the addition of IV acetazolamide to IV loop diuretics compared to placebo in acute decompensated heart failure, regardless of baseline EF and renal function.[10]

Others

Ivabradine reduces heart rate by inhibiting action on "funny" sodium channels (If) responsible for spontaneous diastolic depolarization of the sinoatrial node. It is indicated for use in patients with HFrEF who have persistent symptoms despite receiving maximally tolerated doses of beta-blockers, ACE-I (or ARB) and an MRA, heart rhythm in sinus rhythm, heart rate above 70 beats/min, and EF<35%.[2]

Treatment with Hidralazine+Isosorbid dinitrate is guideline-recommended for HFrEF patients who cannot receive either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers due to intolerance or contraindication.[11] Hydralazine and isosorbide dinitrate should be considered in self-described black patients with LVEF<35% despite treatment with ACE-I (or ARNI), beta-blockers, and MRA or LVEF<45% with dilated left ventricle in NYHA class 3-4 to reduce the risk of HF hospitalization and death.[2]

Although digoxin has no favorable effect on mortality, it can be used for resting rate control in HF patients with atrial fibrillation accompanied by a high ventricular response.

RECENTLY REPORTED ADVANCES FROM HEART FAILURE TRIALS

Soluble Guanylate Cyclase Stimulator

The VICTORIA study evaluated the efficacy and safety of the oral soluble guanylate cyclase stimulator vericiguat in patients with reduced EF and recently decompensated CHF. The incidence of the primary endpoint of death from CV causes or hospitalization for HF was lower in those receiving vericiguat than in those receiving placebo.[12] No reduction in all-cause or CV mortality was seen. Therefore, vericiguat may be considered as an adjunct to standard treatment for HF.

Cardiac Myosin Activator

The GALACTIC-HF study looked at how well and safely the cardiac myosin activator omecamtiv mecarbil worked in both inpatients and outpatients with HF. The primary endpoint of the first HF event or CV death was reduced by 8%. There was no significant reduction in CV mortality. Currently, this drug

is not licensed for use in HF. However, it may be considered in the future as an adjunct to standard treatment for HFrEF to reduce the risk of CV mortality and hospitalization for HF.[13] Disease modifying drugs in important randomized trials in patients with heart failure were summarized in Table.

Table. Disease modifying drugs in important randomized trials in patients with heart failure

ARNI	SGLT2I	ACE-I	ARB	β-blockers	MRA
Sacubitril-Valsartan	Dapagliflozin Empagliflozin Canagliflozin	Captopril Enalapril Lisinopril Ramipril Trandolapril	Candesartan Losartan Valsartan	Bisoprolol Carvedilol Metoprolol Nebivolol	Spironolactone Eplerenone
Other Agents					
Ivabradine, Vericiguat, Digoxin, Hydralazine/Isosorbide dinitrate					

ARNI: Angiotensin receptor-neprilysin inhibitors, SGLT2I: Sodium-glucose cotransporter-2 inhibitors, ACE-I: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, MRA: Mineralocorticoid receptor antagonists

RECENT IMPORTANT STUDIES ON THE TREATMENT OF HF

Circulating NEP and NEP Inhibition in Heart Failure with Preserved Ejection Fraction Study (Phase 4)

To determine biomarker responses to Entresto™ in patients with heart failure with preserved ejection fraction (HFpEF) and high or low serum neprilysin (NEP) levels.[14]

Entresto™ (LCZ696) in Advanced Heart Failure (LIFE Study) (Phase 4)

The primary objective of the study was to determine whether treatment with LCZ696 for 24 weeks would improve Pro-B-type Natriuretic Peptide (NT-proBNP) levels reflecting hemodynamic and clinical status compared to treatment with valsartan in patients with symptomatic, advanced heart failure due to left ventricular systolic dysfunction.[14]

STEP-HFpEF Study (Phase 3)

This study aims to evaluate the efficacy of semaglutide treatment compared to placebo in achieving weight loss in addition to improvement in symptoms, physical limitation and exercise function in patients with CHF and obesity.[15]

Combined Loop-Thiazide Diuretic Therapy (Phase 3)

In the Spain-based study titled "Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC)", which included patients with decompensated HF, it was planned to compare loop diuretic therapy alone with combined loop-thiazide diuretic combination therapy in one arm and loop diuretic therapy with placebo in the other arm and to evaluate the effects on the primary endpoints of body weight and dyspnea.[16]

Randomized Placebo-Controlled Trial of FCM as Treatment for Iron Deficient Heart Failure (Phase 3)

The primary objective of this study was to determine the efficacy and safety of iron therapy using intravenous (IV) ferric carboxymaltose (FCM) compared to placebo in the treatment of heart failure participants with iron deficiency and reduced ejection fraction.[14]

Efficacy and Safety of LCZ696 Compared with Valsartan on Morbidity and Mortality in Heart Failure Patients with Preserved Ejection Fraction (Phase 3)

The aim of this study was to evaluate the effect of LCZ696 compared to valsartan in reducing cardiovascular death and HF hospitalizations in HF patients with preserved ejection fraction.[14]

Evaluating the Safety and Efficacy of Allogeneic Mesenchymal Precursor Cells in the Treatment of Heart Failure (Phase 3)

The primary objective of this study was to determine whether transendocardial delivery of allogeneic human bone marrow-derived MPCs (rexlemestrocel-L) is effective in the treatment of chronic heart failure due to LV systolic dysfunction.[14]

The Assessment of Patiromer for the Management of Hyperkalemia in Individuals Taking Renin-Angiotensin Aldosterone System Inhibitor (RAASi) Drugs for the Treatment of Heart Failure (DIAMOND) (Phase 3)

The aim of this study was to determine whether patiromer treatment of subjects who developed hyperkalemia while receiving RAASi drugs would enable the continued use of RAASi drugs in accordance with HF treatment guidelines and thus reduce the occurrence of the composite endpoint of cardiovascular (CV) death and CV hospitalization events compared to placebo treatment.[14]

Evaluation of Autologous Bone Marrow Mononuclear Cells Using CadiAMP™ Cell Therapy in Patients with Heart Failure After Myocardial Infarction (Phase 3)

This is the first study using the patient's own stem cells in the treatment of patients with systolic dysfunction secondary to ischemic heart disease. Mononuclear cells from the bone marrow are processed on a cell processing platform and administered into the heart with a special method.[14]

Evaluation of the Efficacy and Safety of Human Bone Marrow Derived Stem Cells (CEP-41750) in the Treatment of Chronic Heart Failure (Phase 3)

The primary aim of this study was to determine whether transendocardial administration of human bone marrow-derived stem cells (CEP-41750) is effective in the treatment of chronic heart failure due to LV systolic dysfunction.[14]

Oral Treprostinil in Individuals with Pulmonary Hypertension (PH) Associated with Heart Failure with Preserved Ejection Fraction (HFpEF) (Phase 3)

This study is planned to provide long-term, open-label data on the effect of ongoing long-term oral treprostinil therapy for the treatment of pulmonary hypertension (PH) associated with heart failure with preserved ejection fraction (HFpEF).[14]

FIGARO-DKD Study (Phase 3)

This study examines the cardiovascular and renal effects of finerenone in patients with mild to moderate kidney disease and type 2 diabetes.[17]

CONCLUSION

HF is a chronic disease in which many different mechanisms, humoral systems, and vasoactive agents are involved in its pathophysiology, and despite effective control, the desired efficacy has not yet been achieved with current therapies, and therefore it is difficult to fight. Although much progress has been made in terms of treatment options in the historical process, the discovery of new mechanisms and new drugs effective on these mechanisms enables many new studies in this field. However, it is very difficult to be aware of the many clinical trials in this field and to keep track of them all.

For this reason, we thought that it would be useful to share with our clinicians working in this field by collecting promising studies evaluating new generation drugs that are

still ongoing in this field and whose results will be published soon, as well as treatment options whose benefits have been shown by studies and whose use is supported by current guidelines. It is of vital importance for clinicians to be able to follow these current studies closely, to be familiar with their results, and to know in which indications they are approved and in which patients their use is beneficial in the management of patients with HF.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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